REMARKS

Claim 7 has been amended to obviate a formality matter. No new matter has been added.

Applicants also will contact the Examiner to schedule an interview.

Applicant respond to the prior Office Action as follows.

Rejection of claims under 35 USC 103

Claims 7-10, 14, 15 and 20-22 were rejected over Sasse et al. in view of Greenwald. Applicants respectfully traverse this rejection.

As discussed in Applicants' prior response, in the Rule 132 Declarations of record, it is shown that by coupling tubulysin A with a PEG ester, amide or phenol, the activity of the respective compounds in two cancer cell lines can be dramatically reduced, thus, leading to tubulysin derivatives with lower toxicity.

Furthermore, it is pointed out that Greenwald classifies PEG-drugs in permanently bonded PEG-drugs (cf. chapter 2, page 160) and non-permanently bonded PEG-drugs, i.e. PEG prodrugs (chapter 3, page 160).

According to Greenwald, permanently bonded PEG-drugs comprise PEG linkers of molecular weight 2000 to 5000, i.e. low molecular weight PEG. As can be taken from the Declaration filed November 30, 2006, tubulysin A PEG-derivatives having a PEG linker with high molecular weight, such as 35kDa or 40kDa provide better results with regard to the object of the present invention than low molecular weight PEGs. This finding is by no means rendered obvious by Greenwald suggesting to use permanently bonded PEG-drugs wherein the PEG linker has a molecular weight of from 2000 to 5000. On the contrary, Greenwald ***teaches away*** from the instant invention.

As mentioned above, chapter 3 of the Greenwald publication, PEG prodrugs are disclosed. Greenwald states that a prodrug is a biologically inactive derivative of a parent drug molecule that usually requires an enzymatic transformation within the body in order to release the active drug, and has improved delivery properties over the parent molecule (cf. page 160,

right-hand column, last paragraph). In other words, a prodrug is formed in order to render a parent drug molecule in a condition to enable absorption of the drug molecule in the human body. Once the prodrug has entered the human body, it is enzymatically transformed to release the active drug.

However, this scenario does not apply to the tubulysin derivatives according to the present invention. As stated in paragraph [0003] of the present specification, tubulysins possess an extremely high cytotoxicity. If the tubulysin derivatives released free tubulysins immediately after absorption in the human body, the free tubulysins would immediately exert their cytotoxic effects resulting in extensive cell death of normal cells. As a consequence, such tubulysin prodrugs are not selective and are connected with serious side effects. As stated in paragraph [0004] of the present specification, the object of the present invention is to enhance selectivity of tubulysins.

Applicant has surprisingly found that tubulysin derivatives according to claim 7 are stable in plasma/buffer and, thus, less cytotoxic than natural tubulysins as indicated above with regard to the experimental data set forth in the Rule 132 Declarations of record.. Furthermore, AQpplicant has surprisingly found that once the tubulysin derivatives have entered a cancer cell, free tubulysin is released and can exert its high cytotoxic activity directly in the cancer cell. Accordingly, the compounds according to the present invention provide for drug targeting of tubulysin selectively to cancer cells. These findings are by no means rendered obvious by the publications of Sasse in combination with Greenwald.

Furthermore, as can be taken from the poster attached to the previously submitted Declaration, tubulysin derivatives additionally comprising a cyclodextrin group provide additional benefits. In fact, cyclodextrin-PEG-polymer conjugates of tubulysin show high antiproliferative activity in human cancer cells (cf, table 1), but are significantly less toxic than tubulysin A (cf. table 2). As evident from table 3 and graph 1, cyclodextrin conjugates of tubulysin are better tolerated than vinblastine and tubulysin A and lead to a significant increase in tumor growth delay, inhibit the formation of new tumor cells and at the same time reduce the number of existing tumor cells. It is again pointed out that the Sasse publication does not pertain to tubulysin conjugates and that the Greenwald publication does not disclose cyclodextrin conjugates at all.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Rejection of Claims 12, 13, and 16-19 Under 35 USC 112, First Paragraph

Claims 12, 13, and 16-19 were rejected under 35 USC 112, first paragraph as not being enabling. The rejection is traversed.

The present application fully satisfies the requirements of Section 112, including the "how to make" and "how to use" requirements of Section 112, first paragraph.

For instance, compounds of the invention are described in detail on pages 2-10 of the application. Therapeutic use of compounds of the invention are discussed in detail at pages 10-11.

The skilled worker can readily practice the claimed invention in view of such extensive disclosure.

Moreover, no substantiating reasons have been advanced as to why one skilled in the art could not make and use the claimed invention. Indeed, the discussion above makes clear that one skilled in the art could readily practice the claimed invention in view of Applicants' disclosure.

Respectfully, such a rejection, lacking any supporting evidence or other substantiating grounds is imply not proper. Thus, for example, MPEP §2164.04 states the following (quoting *In re Marzocchi*, 169 USPQ 367):

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Rejection of Claims 1-10 and 12-22 Under 35 USC 112, First Paragraph

Claims 1-10 and 12-22 were rejected under 35 USC 112, first paragraph for lack of written description. The rejection is traversed.

The claims as presented fully satisfy the written description requirements of Section 112. Indeed, for instance, the originally presented provide written description of the current claims.]

In view thereof, withdrawal of the rejection is requested.

Rejection of Claim 7 Under 35 USC 112, Second Paragraph

Claim 7 was rejected under 35 USC 112, second paragraph for recitation of R^{13}.

The objected to term has been deleted from claim 7. It is thus believed the rejection is properly withdrawn.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

By _____

Peter F. Corless
Registration No.: 33,860
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444
Attorneys/Agents For Applicant